ORIGINAL ARTICLE

A randomized controlled trial to compare fentanyl–propofol and ketamine–propofol combination for procedural sedation and analgesia in laparoscopic tubal ligation

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ABSTRACT

Background: Procedural sedation and analgesia is widely being used for female laparoscopic sterilization using combinations of different drugs at varying doses. This study compared the combination of fentanyl and propofol, and ketamine and propofol in patients undergoing outpatient laparoscopic tubal ligation, with respect to their hemodynamic effects, postoperative recovery characteristics, duration of hospital stay, adverse effects, and patient comfort and acceptability. **Settings and Design:** Randomized, double blind. **Methods:** Patients were assigned to receive premixed injection of either fentanyl 1.5 μg/kg + propofol 2 mg/kg (Group PF, n=50) or ketamine 0.5 mg/kg + propofol 2 mg/kg (Group PK, n=50). Hemodynamic data, peripheral oxygen saturation, and respiratory rate were recorded perioperatively. Recovery time, time to discharge, and comfort score were noted. **Statistical Analysis:** Chi-square (χ^2) test was used for categorical data. Student's t-test was used for quantitative variables for comparison between the two groups. For intragroup comparison, paired t-test was used. SPSS 14.0 was used for analysis. **Results:** Although the heart rate was comparable, blood pressures were consistently higher in group PK. Postoperative nausea and vomiting and delay in voiding were more frequent in group PK (P<0.05). The time to reach Aldrete score ≥8 was significantly longer in group PK (11.14±3.29 min in group PF vs. 17.3±6.32 min in group PK, P<0.01). The time to discharge was significantly longer in group PK (105.8±13.07 min in group PF vs.138.18±13.20 min in group PK, P<0.01). Patient comfort and acceptability was better in group PF, P<0.01). **Conclusion:** As compared to ketamine-propofol, fentanyl–propofol combination is associated with faster recovery, earlier discharge, and better patient acceptability.

Key words: *Intravenous sedation, ketamine, laparoscopic tubal ligation, local anesthesia, propofol*

INTRODUCTION

Laparoscopic sterilization in females offers many advantages such as reduced postoperative pain and shortened hospital stay, and is being increasingly performed on an ambulatory basis. In this era of health care cost containment, it is important that anesthetic drugs used for outpatient ambulatory surgery have rapid emergence, less postoperative nausea vomiting (PONV), adequate analgesia, and quick recovery. Local anesthesia with intravenous sedation called as procedural sedation and analgesia (PSA) is widely being used for female laparoscopic sterilization. PSA is a technique of administering sedatives or dissociative agents with analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. Drugs used for PSA should provide an adequate level of sedation while minimizing pain, anxiety, and the potential for adverse drug-related events, maximizing amnesia, and maintaining a stable cardiovascular and respiratory status.[1] Unfortunately, at present, no single agent exists that has all of the aforementioned qualities, so physicians must use combinations of different drugs at varying doses to

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achieve as many of the desired goals as possible. The most recent PSA combination to be described in the literature is that of low-dose ketamine and propofol (ketofol). To our knowledge, ketamine–propofol (ketofol) combination has not been used as procedural sedation and analgesia technique in laparoscopic tubal ligation. The present study was planned to comparatively evaluate postoperative recovery characteristics, duration of hospital stay, patient comfort and acceptability between ketamine–propofol and fentanyl–propofol for PSA in patients undergoing laparoscopic tubal ligation.

METHODS

We conducted this prospective, randomized, double-blinded study in 100 patients of ASA PS grade I, aged 18-45 years, scheduled to undergo laparoscopic tubal ligation (Falope ring placed around a loop of the tube) under PSA at Shrimati Sucheta Kriplani Hospital. The study was approved by the institutional ethical committee and written informed consent was obtained from all participants. Patients who had history of upper respiratory tract infections, asthma, or allergy to propofol or ketamine or receiving treatment for any psychiatric or neuromuscular disease, patients with seizure disorder, acid reflux, hiatus hernia, severe anemia, gross obesity, hepatic, cardiac, or pulmonary diseases were excluded from the study.

Patients were kept fasting overnight. They were randomly allocated by a computer-generated random number table into two equal groups as follows:
Group PF – Fentanyl group (n=50)
Group PK – Ketamine group (n=50)

The sequence was delivered in a sealed envelope on the morning of surgery.

On arrival in the operating room, monitor for pulse oximetry, electrocardiogram (ECG), and non-invasive blood pressure were attached, and the baseline readings recorded. An intravenous catheter was placed and Ringer Lactate was given at the rate of 4 ml/kg/h. Intravenous midazolam 0.02 mg/kg was given to all patients of both groups 5 min prior to the procedure.

Group PF received premixed injection fentanyl 1.5 μg/kg + propofol 2 mg/kg and group PK received premixed injection ketamine 0.5 mg/kg + propofol 2 mg/kg over 30 seconds intravenously. Fentanyl and ketamine were diluted with normal saline to make a volume of 10 ml. The drugs were then mixed with propofol in weight-appropriate dosages to make a final volume of 20 ml. All the drugs were prepared by an anesthesiology resident not involved in the study. Incision site was infiltrated infraumblically with 10 ml of 0.25% bupivacaine. If necessary, propofol was repeated in a dose of 0.5 mg/kg on patient's movement to surgical stimulus.

Heart rate, systolic blood pressure, diastolic pressure, mean arterial pressure, peripheral oxygen saturation, and respiratory rate were monitored and recorded at the following time intervals: Baseline (after 5 min on the OT table), immediately before sedation, 1 min after sedation, and thereafter at 3-min intervals till the end of procedure. ECG and SpO_2 were monitored continuously.

Side effects such as respiratory depression (respiratory rate <8 breaths per minute, apnea longer than 15 seconds or SpO_2<92%), hypotension (more than 20% decrease from the initial value), and bradycardia (heart rate <60 beats per minute), increased secretions, nausea, vomiting, vertigo, visual disturbances, delirium, pruritis and any other side effect were recorded. After the procedure (from end of skin stitching), the time to meet Modified Aldrete score[2] ≥8 was measured. This was recorded as the recovery time. Then, the patients were shifted to the post-anesthesia care unit (PACU). The time to discharge was decided by the Post Anesthetic Discharge Scoring System (PADSS).[3] The time interval between the entry to PACU and the time point at which PADSS achieved a score ≥9 was recorded as the time to discharge. Supplemental drug requirement was also recorded.

Comfort score (1, very unpleasant; 2, unpleasant; 3, neither pleasant nor unpleasant; 4, pleasant; 5, very pleasant) was noted to see patient satisfaction.[4] Medications used for the treatment of PONV and pain were recorded when given in PACU. Postoperative analgesic (injection diclofenac sodium 1.5 mg/kg) was administered when the pain score was ≥3 on the 10-mm Visual Analog Scale. Criteria used for the administration of postoperative antiemetics (injection ondansetron 4 mg) were the presence of mild to severe nausea and/or emesis. All the observations were made by an anesthesiology resident who was unaware of group allocation and blinded to the study drug. The flow of the patients during the study is depicted in Figure 1.

Statistical analysis

Sample size calculation

Power analysis based on pilot cases done prior to the study indicated that at least 40 patients in each group would be required to demonstrate a clinically important difference in PADSS of 20 min with an α=0.05 and a power of 95%. Allowing for the loss of a few patients, 50 patients in each group were recruited.

Chi-square (χ^2) test was used for categorical data. Student's t-test was used for quantitative variables for comparison

between the two groups. For intragroup comparison, paired *t*-test was used. SPSS 14.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. Results are presented as mean±SD. Probability value less than 0.05 was considered significant.

RESULTS

There were no significant differences between the two groups with respect to patient characteristics, mean hemoglobin concentration, and number of patients requiring supplemental propofol and other drugs [Table 1]. Although the heart rate was comparable [Figure 2], systolic blood pressure, diastolic blood pressure, and mean blood pressure were consistently higher in the ketamine group [Figure 3]. The oxygen saturation and respiratory rate were comparable in both the groups (P>0.05).

The time to achieve Modified Aldrete Score of ≥8 in group PF was less (11.14±3.29 min) than in group PK (17.3±6.32 min) [Table 2]. This difference was statistically extremely significant (P<0.01). The mean discharge time in group PF was also shorter (105.8±13.07 min) than in group PK (138.18±13.20 min) [Table 2]. This difference in mean discharge time was statistically extremely significant (P<0.01). No patient had satisfied the home readiness criteria (PADSS ≥9) at 60 min in both the groups. At 90 min, 10% of the patients in group PF had achieved PADSS score of ≥9, but none in group PK had achieved it (P=0.02). The majority of patients (84%) in group PF had achieved home readiness criteria by 120 min, but only 8% in group PK (P=0.01) had done so. Only 12% of patients had to stay in PACU for more than 2 h after anesthesia in group PF. Majority of the patients (86%) in group PK had achieved the PADSS score of ≥9 in 150 min (P<0.01). By 3 h, all of the patients in group PK had achieved home readiness criteria (P<0.01).

The mean comfort score in group PF was higher (3.46±0.70) than in group PK (2.9±0.61) [Table 2]. The difference in comfort scores was statistically significant between groups at all levels [Table 3].

The incidence of apnea (SpO_2<92%), bradycardia (heart rate <60 beats per minute), hypotension (≥20% decrease from the baseline value), and pain abdomen (Visual Analog Scale ≥3) after the procedure was comparable in the two groups [Table 4]. However, there was a significant difference in the incidence of nausea, vomiting, and delay in voiding in the two groups [Table 4]. There were no episodes of increased secretions, vertigo, visual disturbances, delirium, pruritis, and laryngospasm noted in either group during or after the procedure.

DISCUSSION

The present study shows that postoperative recovery was earlier and the duration of hospital stay was shorter in the fentanyl–propofol group as compared to the ketamine–propofol group. Discharge was probably delayed because of adverse effects like nausea and vomiting, and delay in voiding in the ketamine group. Recovery time in the

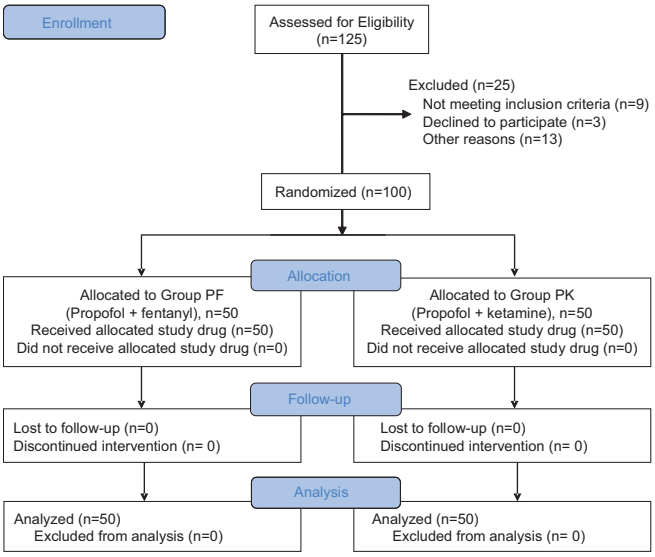

Figure 1: Consort Flow Diagram

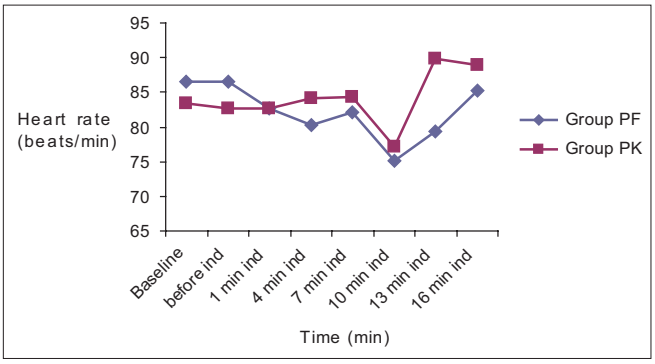

Figure 2: Heart rate

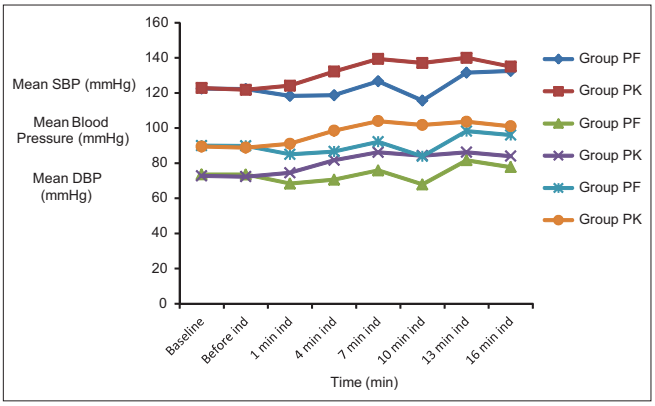

Figure 3: Hemodynamic data

Table 1: Age, weight, hemoglobin, and propofol top-up dose distribution

	Group PF (*n*=50)	Group PK (*n*=50)	*P* value
Mean age (years)	29.14	28.74	0.59
Mean weight (kg)	51.06±9.622	48.30±7.704	0.12
Mean hemoglobin (g/dl)	10.58±0.657	10.70±0.891	0.45
Patients requiring top-up doses	15 (30%)	12 (24%)	0.65
Mean propofol top-up dose (mg)	31±14.75	32±12.10	0.85

Values are Mean ± SD

Table 2: Recovery time, discharge time, and comfort score

	Group PF (*n*=50)	Group PK (*n*=50)	*P* value
Recovery time (min)	11.14±3.295	17.3±6.325	<0.01*
Discharge time (min)	105.8±13.077	138.18±13.201	<0.01*
Comfort score	3.46±0.7	2.9±0.61	<0.01*

*Significant

Table 3: Comfort score

Comfort score	2	3	4	5	Mean±SD
Group PF (*n*=50,%)	4 (8)	21 (42)	23 (46)	2 (4)	3.46±0.7
Group PK (*n*=50,%)	12 (24)	31 (62)	7 (14)	0	2.9±0.61
P value	<0.01*	<0.01*	<0.01*	<0.01*	<0.01*

*Significant

Table 4: Perioperative complications

	Group PF (*n*=50) (%)	Group PK (*n*=50) (%)	*P* value
Apnea	18 (36)	17 (34)	0.83
Bradycardia	3 (6)	4 (8)	0.7
Hypotension	1 (2)	-	0.32
Pain	13 (26)	16 (32)	0.51
Nausea/vomiting	5 (10)	14 (28)	0.04*
Delay in voiding	4 (8)	18 (36)	<0.01*

*Significant

fentanyl group was less than that in the ketamine group, the reason being an earlier return of consciousness. Although this difference was statistically significant ($P<0.01$), a difference of about 6 min is not significant clinically. The patients were more comfortable and more satisfied with the propofol–fentanyl combination as compared to the propofol–ketamine combination due to lesser incidence of nausea and vomiting. Although the heart rate was comparable, blood pressures were consistently higher in the ketamine group, ascribed to the sympathomimetic activity of ketamine.

Most of the major complications of female sterilization result from general anesthesia or from heavy sedation during local anesthesia.[5] Since general anesthesia is known to be responsible for at least one-third of all the deaths associated with sterilization,[5] PSA can be offered as a safer alternative. Goals of PSA include providing an adequate level of sedation while minimizing pain, anxiety, and the potential for adverse drug-related events, maximizing amnesia, and maintaining a stable cardiovascular and respiratory status.[1] The ideal pharmacologic agent for PSA would accomplish all of these goals and would have quick onset and offset, be safe in all age groups, inexpensive, and equally efficacious in multiple routes of administration. PSA combinations commonly used are propofol and low-dose ketamine (ketofol) or propofol with opioids. Although these combinations of drugs for PSA have been used in various procedures, there is no mention of their use in patients undergoing laparoscopic tubal ligation.

Akin *et al*.[6] compared a combination of propofol and fentanyl with propofol and ketamine, but in 40 adult patients undergoing endometrial biopsy. They observed that there was no difference in the recovery times, but the discharge was delayed in the ketamine group. The longer discharge time with ketamine was caused by the higher frequency of vertigo, nausea, and visual disturbances. With regard to patient satisfaction, the propofol–fentanyl group was superior.

Vallejo *et al*.[7] compared postoperative nausea, emesis, analgesia, and recovery between the propofol–ketamine and propofol–fentanyl in outpatient laparoscopic tubal ligation done under general anesthesia. The authors observed no differences with respect to operating times, pain, nausea and vomiting or its treatment, Visual Analog Scale scores, pruritis, and sedation on PACU admission, PACU discharge, and hospital discharge between the two groups. The ketamine group had a higher heart rate, required more pain medication, and had a higher frequency of dreaming on PACU admission than the fentanyl group. These differences became insignificant on discharge. The authors concluded that propofol–ketamine did not improve postoperative nausea, emesis, analgesia, or recovery, compared with the propofol–fentanyl combination.

Badrinath *et al*.[8] investigated the combination of propofol with ketamine at various doses in patients undergoing breast biopsy with local anesthesia. They added 2.5 μg of sufentanil depending on the discomfort and pain experienced by the patient. They also observed that the increased frequency of nausea, vomiting, and visual disturbances due to ketamine prolonged the time to discharge. Jackobson *et al*.[9] used four different drug combinations in patients undergoing termination of pregnancy and reported that propofol–ketamine combination led to the highest frequency of postoperative pain, psychomimetic side effects, and emesis. Although ketamine did not delay discharge, they concluded that propofol–fentanyl was the most suitable combination. Daabiss *et al*.[10] conducted a study to evaluate the effectiveness of different concentrations

of propofol–ketamine in children scheduled for procedural operations. They found delayed recovery and discharge time in patients with higher doses of ketamine due to incidence of clinically significant psychomimetic effects and delayed cognitive function recovery.

To conclude, the combination of fentanyl (1.5 μg/kg) and propofol (2 mg/kg) leads to faster recovery, earlier discharge, and better patient acceptability than the combination of ketamine (0.5 mg/kg) and propofol (2 mg/kg) for procedural sedation and analgesia in patients undergoing laparoscopic tubal ligation.

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